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RESEARCH ARTICLE

Contribution of *LATS1* and *LATS2* promoter methylation in OSCC development

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Abstract The aberrant DNA methylation of the tumor suppressor genes involved in DNA Damage Response (DDR) signaling and cell cycle regulation may lead to the tumorigenesis. Our purpose here is to analyze the promoter methylation and mRNA expression levels of *LATS1* and *LATS2* (*LATS1/2*) genes in OSCC. Promoter methylation status of *LATS1/2* genes was evaluated in 70 OSCC paraffin-embedded tissues and 70 normal oral samples, using Methylation Specific PCR (MSP). *LATS1/2* mRNA expression profiles were also investigated in 14 OSCC patients and 14 normal samples, using real-time PCR. In both candidate genes, promoter methylation assessment revealed significant relationship between cases and controls (OR = 2.24, 95 % CI = 1.40–3.54, $P = 0.001$; *LATS1* and OR = 15.5, 95%CI = 3.64–64.76, $P < 0.001$; *LATS2*). As well as, the evaluation of mRNA expression levels showed decreased expression in OSCC tissues in compare to control tissues. (Mean ± SD 1.74 ± 0.14 in OSCC versus 2.10 ± 0.24 in controls, $P < 0.001$; *LATS1* and Mean ± SD 1.36 ± 0.077 in OSCC versus 1.96 ± 0.096 in controls, $P < 0.001$; *LATS2*). To the best our knowledge, this is the first report regarding the down-regulation of *LATS1/2* through promoter methylation in OSCC. It is suggested to explore the down-stream transcription factors of both genes for finding the molecular mechanism of this deregulation in OSCC.

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Introduction

In developing countries, Oral Squamous Cell Carcinoma (OSCC) is the most prevalent epithelial malignancy influencing the oral cavity (Parkin et al. 2001). OSCC accounts for more than 90 % of all oral neoplasms, therefore it is often used interchangeably with oral cancer (Choi and Myers 2008). The incidence rate of oral cancer is 1.08 and 1.25 per 100,000 in men and women, respectively (Kordi-Tamandani et al. 2010a). Growth of OSCC is a multistep process, resulting from a combination of genetic susceptibility and environmental risk factors including tobacco and alcohol consumption, chronic inflammation and viral infection (Chien et al. 2013). Oncogenes and tumor suppressor genes are the two major groups of pro-tumorigenic genes which promote tumorigenesis whenever up-regulated or down-regulated, respectively (Hanahan and Weinberg 2000). The down-regulation of tumor suppressor genes is preceded through various epigenetic modifications, mutations, loss of heterozygosities and deletions (Perez-Sayans et al. 2009). The epigenetic suppression of genes take place through methylation of CpG islands or histone modifications such as methylation of histone 3, lysine 27 (*H3K27*) (Rad et al. 2016).

Large Tumor Suppressor gene 1 *(LATS1)* and Large Tumor Suppressor gene 2 *(LATS2)*, which located on the 6q25.1 and 13q12.11 chromosomes, respectively; are key tumor suppressor genes in the cell cycle regulation and DDR signaling (Najafi et al. 2016). *LATS1/2* localize to the mitotic apparatus and regulate cell cycle through G2-M arrest and G1-S arrest, respectively (Xia et al. 2002; Li et al. 2003). Novel *Aurora A-Lats1/2-Aurora B* axis directs proper chromosome

segregation and cytokinesis during mitosis (Yabuta et al. 2016; 2011). Also, these genes are main tumor suppressors of hippo signaling pathway which has profound effects on normal cell fate and tumorigenesis (Aqeilan 2013). Furthermore, in response to DNA damage, *LATS1/2* serve as tumor suppressor in *Chk1-Lats2–14–3-3* and *Chk1–Lats2–p21* axes. *Chk1-Lats2–14–3-3* regulates the P-body formation in response to DNA damage and *Chk1–Lats2–p21* axis facilitates apoptosis following high levels of UV radiation, thereby both of the mentioned signals eliminate damaged cells (Scrace and O'Neill 2012; Okada et al. 2011; Suzuki et al. 2013).

Deregulation of *LATS1/2* genes through methylation have been examined in a number of malignancies such as lung cancer, breast cancer, astrocytoma and colorectal cancer (Sasaki et al. 2010; Jiang et al. 2006; Takahashi et al. 2005; Wierzbicki et al. 2013). Our aim was to extrapolate the status of *LATS1/2* promoter methylation and mRNA expression levels in OSCC patients.

Materials and methods

Subject

70 paraffin embedded tissues of OSCC (mean age 54.37 ± 14) and 70 oral mucosa biopsies as controls (mean age 41 ± 14) were obtained from oral and dental disease research center of Zahedan University of Medical Sciences. All clinicopathological information of the patients and the controls filled out by pathologist. The institutional review board approved this study and all participants confirmed the consent form.

DNA extraction and modification

Genomic DNA was isolated from tumor and healthy tissue samples as previously described (Kordi-Tamandani et al. 2010b). Sodium bisulfite modification was performed on 2 μg of DNA to treat un-methylated cytosine to uracil, while leaving methylated cytosine unaltered according to the Wizard® DNA Clean-Up System (Promega, Madison, WI).

Methylation-specific PCR (MSP)

Gene promoters were recognized through online ensemble database. Then sequences of the considered genes were applied to design methylated and un-methylated primers, using MethPrime online software (http://www.urogene.org/cgi-bin/methprimer/methprimer.cgi).

1 μl of bisulfite-modified DNA and 0.5 μL of each primer (10 mmol/l) were added to each AccuPower® HotStart PCR PreMix tube (Cat. No. k-5050, Bioneer Company) which contains lyophilized PCR master mix; Taq DNA polymerase, dNTPs, reaction buffer, tracking dye, and patented stabilizer, then the reaction reached to a final volume of 20 μl using nuclease -free double-distilled water. MSP reactions were subjected to an initial incubation 95 °C for 5 min, followed by 40 cycles (95 °C for 40 s, the annealing temperature for *LATS1*: M = 53 °C, U = 57 °C; *LATS2*: M = 55.5 °C, U = 55 °C for 40 s and extension at 72 °C for 40 s). Final incubation was completed at 72 °C for 10 min. It should be pointed out that a positive control (in vitro methylated and bisulfite-treated human placenta DNA) and a negative control (no sample) were incorporated in all reactions. The designed primers were shown in Table 1.

Analysis of mRNA expression

Total RNA was extracted from fixed paraffin embedded tissues, using the High Pure FFPE RNA Micro Kit) Cat No: 04,823,125,001. As well as, isolation of total RNA from fresh normal samples was performed, using Cinna Pure RNA Purification Kit (Cat No: PR891620). cDNA Synthesis Kit (Fermentas, Cat No: K1621) was utilized to reverse-transcribe 1 μg of RNA to the cDNA in a final volume of 20 μl. To evaluate the gene expression, the

Table 1 Methylation primer sequences and annealing temperatures

Genes	Sequences (5′–3′)	Annealing tem(°C)	Product size
LATS1 M	F:GGAGTTT CGTTTTGTC R: CGACGTAATAACG AACGCCTA	53 °C	138 bp
LATS1 U	F: TAGGTTGGAGTGTGGTGGT R: CCC AACATAATAACAAACACCT	57 °C	121 bp
LATS2 M	F: ATTTCGGTTTATTGTAATTTTC R: AACCAACATAATAAAACCCCG	55 °C	148 bp
LATS2 U	F: TTTGTTTTTT GGGTTTAAGT R: CCAACATAATA AAACCCCA	55 °C	130 bp

M methyl, *U* unmethyl

Table 2 Expression primer sequences and annealing temperatures

Genes	Sequences (5′–3′)	Annealing tem(°C)	Product size
LATS1	F:GTTAAGGGGAGAGCCAGGTCCTT	60 °C	132 bp
	R:TCAAGGAAGTCCCCAGGACTGT		
LATS2	F:ACTTTTCCTGCCACGACTTATTC	60 °C	77 bp
	R:GATGGCTGTTTTAACCCCTCA		
18sRNA	F:GTAACCCGTTGAACCCCATT	60 °C	112 bp
	R:CCATCCAATCGGTAGTAGCG		

cDNA was amplified using specific primer (Table 2) and SYBR green method in Applied Biosystems® 7500 machine (USA). The following optimal thermal condition was applied: 10 min at 95 °C, 35 cycles of 15 s at 95 °C, 30 s at 57 °C, and 45 s at 72 °C. The real- time PCR data was normalized by *18sRNA*.

Statistical analysis

Statistical analyses were performed using SPSS version 23.0 (SPSS, IBM). Chi-square test was applied to analyze the correlation between clinicopathological parameters and promoter methylation status. Methylation status of *LATS1/2* genes and the risk of OSCC development through promoter methylation were assessed using Logistic Regression. The Mann–Whitney test compared mRNA expression data (CT target/Ct housekeeping) between cases and controls. The $p \leq 0.05$ was considered statistically significant.

Results

The promoter of *LATS1/2* gene was methylated in OSCC

Our data revealed that the promoters of *LATS1/2* were methylated in OSCC patients. The methylation frequency of *LATS1* gene was 26(37.14 %) in cases and 58(82.86 %) in controls. *LATS2* gene exposed 29(41.43 %) methylation in cases and 58(82.86 %) in the controls. There was significant association between methylation status of *LATS1/2* genes and the risk of OSCC development [LATS1: OR = 2.24; 95%CI: 1.40–3.54, $p = 0.001$, LATS2: OR = 15.5; 95%CI: 3.7–64.76, p = 0] (Table 3).

Correlation between methylation statuses of *LATS1/2* with clinicopathological data

There was significant correlation between gender and methylation status of *LATS1* ($p = 0.02$). There was no correlation between other clinicopathological data (age, gender and stage) and methylation status of LATS1 and LATS2 (Table 4 and Table 5, respectively).

Decreased mRNA expression levels of *LATS1/2* in OSCC patients

The mRNA expression Analysis of *LATS1/2* genes in OSCC relative to controls revealed the decreased expression of both genes (1.74 ± 0.15 in case vs. 2.10 ± 0.24 in controls in *LATS1* ($p < 0.001$)) and (1.96 ± 0.096 in cases vs. 1.31 ± 0.077 in controls in *LATS2* (p < 0.001)) (Table 6).

Discussion

A recent study has found reduced expression of DDR signaling genes such as *ATM*, *Mre* 11 and *H2AX* in OSCC cell lines (Wang et al. 2012). However, little is known about the

Table 3 Risk of OSCC based on gene promoter methylation

Gene Methylation status	OSCC tissues N = 70	Normal tissues N = 70	OR	95%CI	*P* value	
LATS1	U(ref)	44(62.86 %)	12(17.14 %)	2.24	1.40–3.54	0.001
	M	26(37.14 %)	58(82.86 %)			
LATS2	U(ref)	41(58.57 %)	12(17.14 %)	15.5	3.7–64.76	0.001
	M	29(41.43 %)	58(82.86 %)			

OR odds ratio, *95% CI* 95 % confidence interval, *ref* reference

Table 4 Association between *LATS1* gene promoter methylation and clinicopathological parameters in patients with OSCC and health controls

Characteristics	Control (n = 70)		P	Case (n = 70)		P
	Methylation status*			Methylation status		
	M n(%)	U n(%)		M n(%)	U n(%)	
Age			0.97			0.76
> 50	48(82.8 %)	10(83.4 %)		22(84.6 %)	36(81.1 %)	
< 50	10(17.2 %)	2(16.7 %)		4(15.4 %)	8(18.2 %)	
Gender			0.03**			0.02**
Male	29(50 %)	10(83.3 %)		10(38.5 %)	29(56.9 %)	
Female	29(50 %)	2(16.7 %)		16(61.5 %)	15(34.1 %)	
Stage			0.11			
I	12(20.7)	4(33.3 %)				
II	17(29.3 %)	0(0 %)				
Well differentiated	28(48.3 %)	7(58.3 %)				
Metastatic	1(1.7 %)	1(8.3 %)				

Chi-square test

**M* methyl, *U* unmethyl

***significant*

LATS1/2 genes in oral cavity cancers. The data of the current study elucidated that DNA methylation mediates reduction in mRNA expression levels of *LATS1/2* in OSCC patients.

LATS1/2 protein kinases control cell fate through different signaling pathways (Yabuta et al. 2013). Overexpression of *LATS1* results in G (2)/M arrest through inhibiting the *CDC2* kinase activity, whereas *LATS2* regulates G1/S transition via modulating the kinase activity of Cyclin *E/CDK2* (Xia et al. 2002; Li et al. 2003). Furthermore, at the onset of mitosis, *LATS2* influences spindle formation to control precise segregation (Li et al. 2003). In response to mitotic damage, *LATS2* prevents damage through inhibiting *Mdm2*, which in turn stabilizes *p53* protein (Aylon et al. 2006). Another impressive role of *LATS2* in response to damage is apoptosis triggering

Table 5 Association between *LATS2* gene promoter methylation and clinicopathological parameters in patients with OSCC and health controls

Characteristics	Control (n = 70)		P	Case (n = 70)		P
	Methylation status*			Methylation status		
	M n(%)	U n(%)		M n(%)	U n(%)	
Age			0.97			0.5
> 50	48(82.2 %))	10(83.3 %)		23(79.3 %)	35(85.4 %)	
< 50	10(16.7 %)	2(17.2 %)		6(14.6 %)	6(20.7 %)	
Gender			0.4			0.3
Male	31(53.8 %)	8(66.7 %)		14(48.3 %)	25(61 %)	
Female	27(46.6 %)	4(33.3 %)		15(51.7 %)	16(38 %)	
Stage			0.10			
I	15(25.9 %)	1(8.3 %)				
II	16(27.6 %)	1(8.3 %)				
Well differentiated	26(44.8 %)	9(75 %)				
Metastatic	1(1.7 %)	1(8.3 %)				

Chi-square test

**M* methyl, *U* unmethyl

Table 6 Comparison of relative gene expression for *LATS1* and *LATS2* genes between patients with OSCC and healthy controls

Genes		No.	Mean ± SD	p-Value[a]
LATS1	Cases	14	1.74 ± 0.15	0.001
	Controls	14	2.10 ± 0.24	
LATS2	Cases	14	1.31 ± 0.077	0.001
	Controls	14	1.96 ± 0.096	

[a] Mann-Whitney-Test

through phosphorylation of *ASPP1* in *Lats2-ASPP1-p53* axis which shunts *p53* to pro-apoptotic promoters and promotes apoptosis (Aylon et al. 2010). Unlike *LATS2* gene, *LATS1* gene achieves mentioned activities through *RASSF1A* → *MST2* → *LATS1* pathway, which finally induces apoptosis through blocking *Mdm2* and leading to *p53* stabilization (Matallanas et al. 2011).

LATS1/2 on the hippo signaling pathway phosphorylate *YAP/TAZ* dimer which leads to shift the dimer from cytoplasm to nuclear. Eventually, *YAP/TAZ* stimulate transcription of *TEAD* factors which affect cell proliferation, metastasis and epithelial-to-mesenchymal transition (EMT) (Piccolo et al. 2014). Moreover, the phosphorylation of *LATS2* on *Ser380* by *Aurora A* and its interaction with *Aurora B* in *ALB* pathway (*Aurora A-Lats1/2-Aurora B* axis) guarantee centrosome separation in response to mitotic signals. On the other hand, *LATS2* could be phosphorylated on *Ser83* by *Aurora A* which led to *LATS2* centrosomal localization during interphase for centrosome maturation. Intriguingly, after microtubule damage *ALB* pathway prevents from aneuploidy through phosphorylation of *Aurora B* by *LATS1/2* genes which form a tetraploidy checkpoint together with *P53* (Yabuta et al. 2016; Furth and Oren 2011). Recently, Yabuta et al. (2016) reported *LATS1/2* phosphorylate inner centromere protein *(INCENP)* at S894 which in turn activates *Aurora B* that this is necessary for proper cytokinesis completion in multipolar division (Yabuta et al. 2016).

LATS1/2 genes control cell cycle gates through abovementioned pathways; therefore their down-regulation through promoter methylation could give rise to various malignancies. Recently, it was demonstrated that reduced mRNA expression levels of *LATS1/2* genes result in decreased entry to the quiescence stage (G0) and increased of cell growth (Sadasivam and DeCaprio 2013). In line with this study, A number of articles displayed the down-regulation of *LATS1/2* genes through promoter methylation in different types of malignant and benign tumors including lung cancer, human astrocytoma, breast cancer, colorectal cancer and pterygium (Najafi et al. 2016; Sasaki et al. 2010; Jiang et al. 2006; Takahashi et al. 2005; Wierzbicki et al. 2013). The status of *LATS1/2* promoter methylation and mRNA expression changes between these tumors has been summarized in Table 7.

Until now, previous studies have indicated the promoter methylation and mRNA expression profiles of *P14ARF, MGMT, CDH1, APC, ATM, P15INK4b, P16INK4a, FADD, FAS, ERK* and *RAF1* in OSCC (Kordi-Tamandani et al. 2010b; Rigi-Ladiz et al. 2011; Kordi-Tamandani et al. 2012; Saberi et al. 2014; Kordi-Tamandani et al. 2014). Taken together, the outcomes of the current study presented novel methylation markers for designing drugs that modify methylation statuses in OSCC (Mikeska and Craig 2014).

In conclusion, our results showed the down-regulation of *LATS1/2* genes through methylation of their promoters. We propose to use advanced molecular techniques such as RNAseq in various genetic populations to identify the down-stream transcription factors of both genes for exploring the molecular mechanism of these deregulations in OSCC (Zhang et al. 2013; Tuch et al. 2010).

Table 7 The contribution of *LATS1* and *LATS2* promoter methylation in different type of malignant and benign tumors

Author	Cancer Gene	Promoter Methylation	Expression	
Takahashi et al. 2005	Breast*	*LATS1* *LATS2*	17⁄30 (59/7 %) 15⁄30 (50 %)	Decrease
Jiang et al. 2006	Astrocytoma*	*LATS1* *LATS2*	56⁄88 (63/66 %) 63⁄88 (71/5 %)	Decrease
Sasaki et al. 2010	Lung*	*LATS1* *LATS2*	160⁄203 (78/8 %) 95⁄119 (79/8 %)	Decrease
Wierzbicki et al. 2013	Colorectal*	*LATS1*	25⁄44 (57 %)	Decrease
Najafi et al. 2016	Pterygium**	*LATS1* *LATS2*	66⁄70 (94/28 %) 69⁄70 (98/57 %)	Decrease

*malignant

**benign

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Compliance with ethical standards

Conflicts of interest The authors declare no conflict of interest.

Research involving human participants All procedures performed in studies involving human participants was in accordance with the ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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